We are investigating a stable biomarker, the ratio of different chromosome aberrations, which is specific to densely-ionizing radiation such as alpha particles and neutrons.
We are studying this biomarker in blood samples of workers who were exposed several decades ago to plutonium and to gamma rays at the Mayak nuclear facility

A HIGH-LET SPECIFIC BIOMARKER IN THE MAYAK WORKER COHORT

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Why would anyone be interested in a biomarker for high-LET radiation?

Molecular Epidemiology of High-LET Radiation

- Radon
- Plutonium workers
- Aircrew / frequent flyers
- Hiroshima

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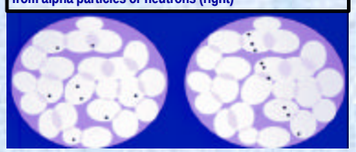
We are interested in ratios of yields between different types of radiation-induced exchange aberrations, in which the different aberrations have very different mean distances between the initial breaks underlying the exchange

Intra-arm:	Inter-arm:	Inter-chromosome:
Very short distance between initial breaks	Intermediate distance between initial breaks	Long distance between initial breaks

next

The reason for looking at ratios of these different types of chromosome aberrations is that the densely ionizing radiation such as alpha particles or neutrons produce double-strand breaks that are much closer together than does x rays

Cartoon of DNA double-strand breaks (DSB) produced by x rays (left) in chromosome domains in the nucleus, and from alpha particles or neutrons (right)



Radiations producing DSBs that are, on average, near to each other will have an extra preference for the production of chromosome aberrations originating from pairs of nearby DSBs.

This is the theoretical basis of the biomarker!

next

Relevant Chromosome Aberration Types

	Inter-chromosomal	Intra-chromosomal inter-arm	Intra-chromosomal intra-arm
Stable (non lethal)	Translocation	Pericentric Inversion	Paracentric Inversion
Unstable (lethal)	Dicentric	Centric Ring	Interstitial Deletion

Examples of Ratios that can be Measured:

F: Intra-chromosomal [inter-arm] *vs* inter-chromosomal

G: Intra-chromosomal [intra-arm] *vs* intra-chromosomal [inter-arm]

H: Intra-chromosomal [intra-arm] *vs* inter- chromosomal

next

Long term stability of chromosomal aberration ratios

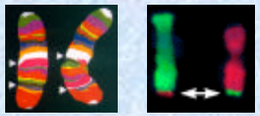
- Unstable aberrations decrease rapidly with time, so are unsuitable as long-term biomarkers
- Stable aberrations also decrease, though more slowly, with time
- What about ratios of stable aberrations?

Measured F values in A-bomb survivors at Hiroshima are pretty stable over many years…

Blood taken in…	*F* value
1968 - 69	6.8 ± 0.4
1977 - 91	5.7 ± 0.4
1989 – 90	6.2 ± 0.7
1977 - 98	7.2 ± 0.2

The *H* ratio

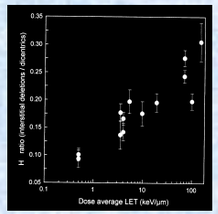
The H ratio refers to aberrations with the shortest separation of breaks (intra-arm) vs aberrations with the largest separation of breaks (inter-chromosomal), so it would be expected to show the largest LET effect



Shown above are intra-arm and inter-chromosomal aberrations as visualized with FISH (chromosome painting). Note that intra-arm aberrations cannot be seen with a whole-chromosome paint, and new FISH banding techniques have to be used

next

Measured *H* ratios



From Bauchinger (1998)

Note the strong LET dependence

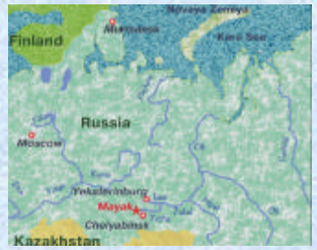
Measured ratios of low-LET to high-LET *H* values

- Livermore: 1.9 ±0.5
- Munich: 3.0 ±1.0
- Columbia: 2.5 ±0.9
- MRC Harwell: 4.1

* *Note all these measurements are for unstable aberrations*

next

We are investigating this biomarker using blood drawn from individuals who worked in the 1950's and 1960's at the Plutonium production plant at the Mayak Nuclear Complex, in the Southern Ural Mountains



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We are initially measuring these ratios in lymphocytes taken from the blood of workers who had very high plutonium (high-LET alpha-particle) body burdens, and comparing with the same ratios from individuals who had high gamma-ray (low-LET) exposures.

Specifically, we are looking at aberrations in lymphocytes from individuals with a plutonium body burden of more than 300 nCi, and also from individuals who received a whole body dose of more than 2 Gy.

Metaphase slide preparations, and initial cytogenetics are being done in Ozyorsk, while the FISH analysis is being done at Columbia University

next

CONCLUSIONS

This Russian-US collaborative project, sponsored by the US Department of Energy, has two goals:

- To develop and validate in-vivo a practical long-term, stable biomarker for exposure to densely-ionizing radiations such as alpha particles and neutrons. Such a tool would be of considerable help to epidemiologists in trying to assess the long term consequences of past low-level exposures to radon, to plutonium, and to neutrons
- Our second goal is to use this biomarker, and its LET dependence, as a probe of mechanisms of chromosome aberration formation, and thus towards a better mechanistic understanding of the potential carcinogenic effects of low levels of ionizing radiation.